

Comparison of venous thromboembolic complications following urological surgery between patients with or without cancer

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Cite this article as: Thomsen FB, Pedersen TB, Berg KD, Clark PE, Lund L. Comparison of venous thromboembolic complications following urological surgery between patients with or without cancer. Turk J Urol 2020; 46(4): 277-81.

ABSTRACT

Objective: Guidelines recommend 4 weeks of thromboembolic prophylaxis in patients who undergo major surgery for solid malignancies. However, there are limited head-to-head comparisons of risk of venous thromboembolic complications in patients with and without cancer undergoing similar surgical procedures. The purpose of this study was to compare risk of venous thromboembolic complications following major renal surgery and cystectomy between patients with and without cancer at the time of surgery.

Material and methods: In the nationwide Danish National Patient Registry, which captures all hospital contacts, including surgical procedures, we identified 8,645 patients who underwent major renal surgery (4,273 without cancer and 4,372 with cancer) and 2,164 patients who underwent cystectomy (359 without cancer and 1,805 with cancer) in 2000–2009. The rate of venous thromboembolic events within 6 months from surgery was compared for patients with and without cancer after stratification on organ using Chi-squared test.

Results: There was no difference in the rate of venous thromboembolic complications within the first 6 months after major renal surgery (0.4% and 0.3% [p=0.91]) or cystectomy (1.3% and 0.8% [p=0.44]) for patients with and without cancer. The cost for 28 days of Tinzaparin 4,500 IE administered by the patient was €112, whereas the cost if administered by a community nurse was €1,988.

Conclusions: Our study questions the different recommendations in thromboembolic prophylaxis between patients with and without cancer after major renal surgery and cystectomy.

Keywords: Cancer; cystectomy; nephrectomy; thromboembolic prophylaxis.

Introduction

Venous thromboembolisms (VTEs), composed of deep vein thrombosis and pulmonary embolism, are potentially life-threatening complications after surgery and are the most common causes of death within the first 30 days after cancer surgery.^[1] VTEs are promoted by venous stasis, hypercoagulable states, and vascular injury, that is, Virchow's triad and risk factors, include major surgery, age, previous VTEs, and concurrent malignancy.^[2,3]

The risk of VTEs can be reduced with mechanical and medical prophylaxis and early mobilization.^[4] Higher dose thromboembolic prophylaxis for longer duration reduces the

risk of postsurgical VTEs after larger abdominal and pelvic procedures.^[5,6] Consequently, in 2009, the Danish Society for Thrombosis and Hemostasis recommended 4 weeks of thromboembolic prophylaxis in all patients who underwent surgery for solid malignancies.^[7] This recommendation is in line with other national organizations.^[4]

However, there is a lack of head-to-head comparisons of risk of VTEs between patients with and without cancer undergoing similar surgical procedures. The objective of this study was to compare risk of VTEs after major renal and bladder surgery between patients with and without cancer in a nationwide observational study using Danish register-based data.

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Submitted:

29.01.2020

Accepted:

20.04.2020

Available Online Date:

08.05.2020

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Material and methods

Data collection

The Danish National Patient Registry (DNPR) was established in 1976 and contains information for all hospital contacts, inpatient as well as outpatient, for each Danish citizen.^[8] In this study, we identified all patients in DNPR who underwent major renal surgery, that is, nephrectomy, heminephrectomy, other kidney resections, and reconstructive surgery (International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10]: KKAC00-21, KKAD00-51, KKAD96-97, KKA00-11, and KKAH30-41) or cystectomy (ICD-10: KKCC00-97) between January 1, 2000 and December 31, 2009.

Comorbidity was assessed according to the Charlson comorbidity index and on the basis of data extracted from the DNPR 10-years before the procedure (ICD-10: cancer [DC00-DC97], infected with human immunodeficiency virus [DB20], diabetes mellitus [DE10-DE14], dementia [DF00-03], ischemic heart diseases [DI21-DI25], heart failure [DI50], cerebrovascular disease [DG45, DG46, DI60-DI69], vascular diseases [DI70-DI79, DI260, DI269, DI802, DI803, DT817C, DT817D], chronic respiratory disease [DJ40-DJ47], liver diseases [DK70-DK77], and connective disorders [DM30-DM36]).^[9] Furthermore, cancer diagnosis after the procedure (ICD-10: renal cancer [DC64], upper-urothelial cancer [DC65, DC66], and bladder cancer [DC67]), and VTE events within 6 months following the procedure (ICD-10: deep vein thrombosis [DI802, DI803, DT817C] and pulmonary embolism [DI260, DI269, DT817D]) were extracted from the DNPR. Causes and dates of deaths were extracted from the Danish Cause of Death Registry. Patients aged younger than 18 years and patients with a history of cancer unrelated to the surgery in question within 10 years from date of the procedure were excluded. Data extraction from database did not require consent from patients or approval from the local Ethical committee because no data were patient-related information.

The estimated daily expense in euros (€) for Tinzaparin 4.500 IE was €4, whereas the expense for a visit by a community nurse was €67.

Main Points:

- The rates of thromboembolic complications associated with renal surgery were in general low in the Danish population when investigated in the period 2000–2009.
- There are no differences in thromboembolic complications between cancer-related and non-cancer-related renal surgery.
- There are, however, great differences in thromboembolic prophylaxis in the 2 patient groups, and standardized guidelines are needed.

Statistical analysis

Rate of VTEs within 6 months from the surgical procedure for patients with and without cancer was compared with Chi-squared test and logistic regression with results presented as odds ratios (ORs) with 95% confidence intervals (CIs). The results were stratified on organ (kidney and bladder). All tests were two-sided, and the significance level was set to $p < 0.05$. Statistical analysis was performed with R (R Foundation for Statistical Computing, Vienna, Austria). The study was approved by Odense Patient data Explorative Network (Study ID OP_421).

Results

In total, 10,809 eligible patients were identified in DNPR and were included in the study (Figure 1). Patients without cancer were younger but had more comorbidity compared with patients with cancer (Table 1).

There was no difference in the rate of VTEs within the first 6 months after major renal surgery (0.4% and 0.3% [$p=0.91$]) or cystectomy (1.3% and 0.8% [$p=0.44$]) of patients with and without cancer (Table 2). No VTE-related deaths were recorded in the study.

After renal surgery, the OR for VTE in patients with cancer was 1.04 (95% CI, 0.51–2.13; $p=0.91$) compared with patients without cancer. Moreover, the OR of VTE following cystectomy was 1.60 (95% CI, 0.56–6.75; $p=0.45$) for patients with cancer compared with patients without cancer. The low number of VTE events precludes meaningful adjustment for differences in age and comorbidity.

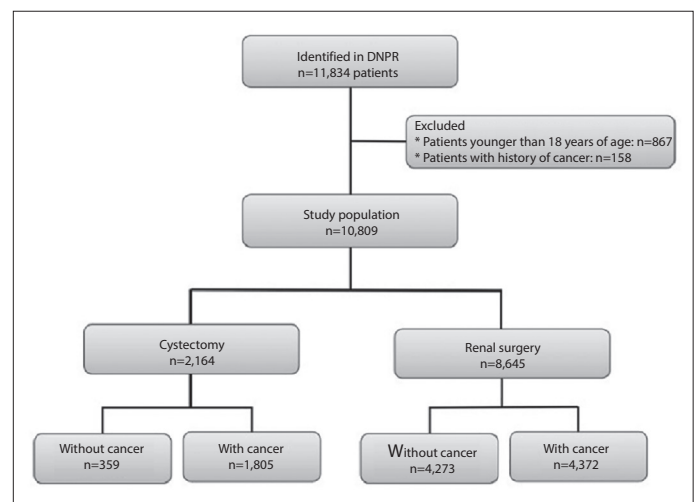


Figure 1. Workflow for patients identified in the Danish National Patient Registry and stratified for inclusion

Table 1. Baseline characteristics of patients who underwent cystectomy or renal surgery in 2000–2009 identified in the Danish Patient Registry

Characteristics	Cystectomy		*p	Renal surgery		*p
	Without cancer (n=359)	With cancer (n=1,805)		Without cancer (n=4,273)	With cancer (n=4,372)	
Age, n (%) years			<0.001			0.001
18–49	68 (19)	89 (5)		1,474 (35)	419 (10)	
50–59	74 (20)	418 (23)		794 (19)	945 (22)	
60–69	120 (33)	832 (46)		955 (22)	1,362 (31)	
70–79	94 (26)	451 (25)		793 (19)	1,244 (28)	
80+	3 (1)	15 (1)		257 (6)	11 (9)	
Year of surgery, n (%)			0.001			<0.001
2000–2001	14 (4)	152 (8)		384 (9)	396 (9)	
2002–2003	85 (24)	294 (16)		940 (22)	598 (14)	
2004–2005	54 (15)	320 (18)		769 (18)	813 (19)	
2006–2007	72 (20)	389 (22)		855 (20)	908 (21)	
2008–2009	134 (37)	650 (36)		1,325 (31)	1,657 (38)	
Charlson comorbidity index, n (%)			<0.001			<0.001
0	292 (81)	1,709 (95)		3,395 (79)	3,972 (91)	
1	29 (8)	66 (4)		387 (9)	172 (4)	
2+	38 (11)	30 (1)		491 (11)	228 (5)	
Education, n (%)			0.59			<0.001
Low	153 (42)	700 (40)		1,685 (39)	1,810 (41)	
Middle	132 (37)	730 (40)		1,279 (30)	1,486 (34)	
High	66 (18)	331 (18)		1,136 (27)	866 (20)	
Unknown	8 (2)	44 (2)		176 (4)	206 (5)	
Procedure, n (%)						<0.001
Nephrectomy, n (%)	—	—		2,924 (68)	4,078 (93)	
Heminephrectomy, n (%)	—	—		290 (7)	213 (5)	
Other kidney procedure, n (%)	—	—		1,059 (25)	81 (2)	

*Chi-squared test

Table 2. Venous thromboembolic event within 6 months from the date of surgery

	Cystectomy		p*	Renal surgery		p*
	Patients without cancer n=359 n (%)	Patients with cancer n=1,805 n (%)		Patients without cancer n=4,273 n (%)	Patients with cancer n=4,372 n (%)	
VTE						
Any	3 (0.8)	24 (1.3)	0.44	15 (0.3)	16 (0.4)	0.9
DVT	3 (0.8)	15 (0.8)		11 (0.3)	8 (0.2)	
PE	0 (0)	9 (0.5)		4 (0.1)	8 (0.2)	

*Chi-squared test. VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism

The estimated cost for 28 days of Tinzaparin 4,500 IE administered by a community nurse is €1,988. Thus, the cost of prevent-

ing 1 VTE event following cystectomy in patients with bladder cancer assuming 4 weeks of thromboembolic prophylaxis reduc-

es the risk with 56%^[10] (i.e., 13.44 of the 24 events prevented) is €266.9896.

Discussion

In this register-based, observational study, the rate of VTEs within the first 6 months following major renal surgery or cystectomy was low and similar in a head-to-head comparison between patients with and without cancer.

The main limitations of this study are the lack of information on thromboembolic prophylaxis and missing information on other potential risk factors for VTEs—obesity, smoking, etc. In addition to this, lack of information on the duration of the surgeries and post-surgery rehabilitation in both cancer-related and non-cancer surgeries is also an important limitation. On the other hand, the validity of VTEs in the DNPR is high (88% accuracy [95% CI, 80–93]).^[11] The apparent lack of a difference in the rate of VTEs between patients with and without cancer could partly be attributable to patients without cancer having more comorbidity. On the other hand, patients without cancer were younger. Furthermore, only VTEs in patients who were diagnosed at a hospital were captured. Thus, asymptomatic VTEs and symptomatic VTEs treated by general practitioners have not been identified. Another potential bias is incomplete coding to the DNPR at discharge after the index admission. In contrast, the practice in Denmark is to confirm all symptomatic VTEs with ultrasound, and we have no reason to assume that there was a systematic difference in the referral, workup, or subsequent coding between patients with and without cancer who developed symptoms of a VTEs.

The VTEs' rates of 0.3%–0.4% following major renal surgery and 0.8%–1.3% after cystectomy is somewhat lower compared with the literature.^[12–14] The rate of VTEs following renal surgery and cystectomy has previously been reported in the range of 1%–1.7% and 2.9%–6%, respectively. Potential explanations for this are differences in study methodology as only hospital captured VTEs are included in this study. Other reasons may be variations in time to mobilization, length of hospital admission, and outpatient check-ups. In Denmark, the median time of hospital admission following nephrectomy was 4 days in 2008–2012 and 19 days following cystectomy in 2001–2005.^[15,16] Comparable numbers from other western countries in comparable time periods were 3–10 days following nephrectomy^[17,18] and 6–16 days following cystectomy.^[17–20] Another possibility is that patients in Denmark received a longer duration thromboembolic prophylaxis compared with other countries. During the period studied, most patients received thromboembolic prophylaxis while they were hospitalized, whereas some Danish urological centers also administered 7 days post-discharge thromboembolic prophylaxis following cystectomy (personal communication).

This is, to the best of our knowledge, the first head-to-head study comparing risk of VTEs for patients with and without cancer after major renal surgery and cystectomy. A higher risk of VTE among patients with cancer compared with patients without cancer at the time of surgery have been found—also within the urological field.^[3,12] In a large register-based study, including 1,653,275 cases who underwent different urgent or elective surgical procedures, the overall rate of symptomatic VTEs within 3 months of surgery was 0.8%, with up to 65% of VTE occurring after discharge.^[3] The rate of VTEs for high-risk procedures such as nephrectomy and cystectomy was 2%–3%. In a multiple logistic regression analysis, the presence of malignancy was associated with 1.7 increased odds of VTEs when compared with similar procedures in patients without cancer. However, this study did not compare risk of VTEs stratified on procedure, and as such, patients with cancer are likely *a priori* higher risk of developing a VTE compared with patients without cancer because they underwent more extensive surgery.

The length of postsurgical thromboembolic prophylaxis has been recommended to be extended to 4 weeks in patients with cancer.^[4,7] This recommendation is supported by a recent meta-analysis demonstrating that extended (2–6 weeks) thromboembolic prophylaxis is associated with a relative risk of 0.44 for development of VTEs compared with conventional (up to 2 weeks) thromboembolic prophylaxis.^[10] Furthermore, extended thromboembolic prophylaxis had no impact on major bleeding or 90-day-mortality. The lower risk of VTE was, however, primarily driven by a reduced incidence of deep vein thrombosis, as the incidence of pulmonary embolism was not lowered by extended thromboembolic prophylaxis. As discussed previously, we could not confirm these findings. Instead, our results indicate that patients without cancer have a comparable risk of VTEs as patients with cancer. This indicates that the higher risk of VTEs for patients with cancer is related to the procedure and not the underlying disease. As such, our results indicate that patients undergoing major renal surgery and cystectomy should be treated equally irrespective of the presence or absence of malignancy. However, given the low rate of symptomatic VTEs and the high estimated cost of preventing one VTE, there is a need to identify new risk factors for VTEs to optimize which patients should receive extended thromboembolic prophylaxis.

In conclusion, in this register-based, observational study, we found low incidences of VTEs complications after major renal surgery and cystectomy and no difference between patients with and without cancer. Our study questions the current difference in thromboembolic prophylaxis between patients with and without cancer after these procedures. Furthermore, it highlights the need for future studies to address the optimal duration of

such prophylaxis and finding new and additional risk factors for VTEs to personalize treatment.

Ethics Committee Approval: Data extraction from database did not require approval from the local Ethical committee because no data were patient-related information.

Informed Consent: Data extraction from database did not require consent from patients because no data were patient-related information.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.B.T., T.B.P., K.D.B., P.E.C., L.L.; Design – F.B.T., T.B.P., K.D.B., P.E.C., L.L.; Resources – L.L.; Materials – F.B.T., L.L.; Data Collection and/or Processing – F.B.T., L.L.; Analysis and/or Interpretation – F.B.T., L.L.; Literature Search – F.B.T., L.L.; Writing Manuscript – F.B.T.; Critical Review – T.B.P., K.D.B., P.E.C., L.L.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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